vessels or to a peripheral vein in a human patient in need of relief from symptoms of angina, said unit dose comprising from about .008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.

36. The method of claim 35, wherein said unit dose is administered to one or more coronary vessels.

37. The method of claim 35, wherein said unit dose is administered to a peripheral vein. --

REMARKS

The amendment to the specification at page 22, line 2 merely corrects a typographical error in the word "optimal". Accordingly, the amendment to the specification does not add new matter. The amendments to the claims do not add new matter. Specifically, claim 19, which has been amended to recite that the "unit dose produces a therapeutic benefit **against coronary artery disease"** is supported by the preamble of independent claim 17 ("A method for treating coronary artery disease") from which it ultimately depends. Claims 20 and 21 have been amended by deleting extraneous language. Newly added claim 35 is directed to a method for treating angina in a human patient comprising administering a unit dose of the present invention to one or more coronary vessels or to a peripheral vein. Support for a method for treating angina is found throughout the specification, including at page 21, line 29 to page 22, line 3 ("The human patient in need of treatment for coronary artery disease is typically a human patient with coronary artery disease who remains **symptomatic with angina** despite optimal medical management"); emphasis added in bold. Support for the effectiveness of the claimed method is found throughout the specification, including the data from the SAQ questionnaire at page 7, lines 16-19, wherein an increase in score of

8 points is considered significant ("For angina stability, the mean score increased by 32.1 to 46.2 at 2 months; and by 16.7 to 23.2 at 6 months. For angina frequency, the mean score increased by 20.0 to 32.9 at 2 months; and by 11.4 to 36.7 at 6 months."). Support for administering the unit dose of FGF-2 to one or more coronary vessels or to a peripheral vein is found throughout the specification, including at page 21, lines 24-29 ("one or more, typically two, patent coronary vessels or a peripheral vein of a human patient"); at page 22, line 4 ("A preferred coronary vessel is a coronary artery") and lines 5-8 ("Suitable peripheral veins for administering the unit dose composition include those peripheral veins found throughout the human body that are routinely used by treating physicians and nurses for administration of fluids and medicaments."). Claims 36 and 37, which are directed to the method of claim 35, wherein the unit dose is administered to one or more coronary vessels or to a peripheral vein, respectively, is supported by the same disclosures in the specification that support the recitation of these two alternatives in claim 35. Accordingly, the amendments to the claims also do not add new matter.

Summary of the Bases for Rejection

The specification is objected to because at page 21, line 28, the Patent Office contends that the recitation of "patent" should be "patient."

The Abstract is objected to because of its length and alleged use of legal phraseology.

Claims 1-34 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite.

Claims 1-9 are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by U.S. Pat. 5,155,214 (Baird).

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Claims 1-34 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Baird, in view of Sellke (Soc. of Thoracic Surgery, 65:1540-1544, 1992) and Uchida (Am. Heart J., 130(6): 1182-1188, Dec. 1995).

The Applicant will address each of the above-stated bases for objection or rejection in Sections I-V, respectively, which follow. For the convenience of the Patent Office, a copy of all pending claims is attached hereto as Exhibit A.

I. Objection to the Specification

The Patent Office objects to the specification because of the Applicant's recitation at page 21, line 28, of the word "patent" which the Patent Office contends should be "patient". The Applicant respectfully disagrees. The phrase containing the term "patient" and giving rise to the objection recites as follows:

> administering a safe and therapeutically effective amount of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof to one or more, typically two, **patent** coronary vessels or a peripheral vein of a human **patient** . . .
>
> [Specification at page 21, lines 26-28; emphasis added in bold.]

The Applicant respectfully submits that the term "**patent**" (shown in bold above) is understood by those skilled in the medical arts to mean "**open, unobstructed, or not closed**," when used in conjunction with a coronary vessel. [Exhibit B: Dorland's Illustrated Medical Dictionary, 24th Ed., W.B. Saunder's Co., Phila. PA, 1965 at page 1111; emphasis added in bold.] The correctness of the Applicant's use of the term "patent" is even more clear when one considers that the word "patient" is already used at the end of the phrase. Thus, the word "patent" is properly used in the specification at page 21, line 28. Accordingly, the objection to the specification is based upon a factual error and should be withdrawn.

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II. Objection to the Abstract

The Patent Office objects to the Abstract because of its length and its alleged use of legal phraseology. The Patent Office states that "[t]he abstract should be in narrative form and generally limited to a **single paragraph** on a **separate sheet** within the range of **50 to 250 words**." [Official Action at page 2.] The Patent Office continues that "[i]t is important that the abstract **not exceed 250 words** in length since the space provided for the abstract on the computer tape used by the printer is limited." [Official Action at page 2.] The Applicant respectfully submits that the Patent Office may be confusing the Applicant's Abstract with another, since on its face, the Applicant's Abstract is a **single paragraph** on a **separate sheet** having **216 words** (*i.e.*, within the prescribed range of 50 to 250 words). Thus, the computer tape should not run out of space printing the Applicant's Abstract.

The Patent Office next contends that "[t]he form and legal phraseology often used in patent claims, such as 'means' and 'said' should be avoided." [Official Action at page 2.] The Applicant respectfully submits that the words "means" and "said" never appear in the Applicant's Abstract. In fact, the word "means" never appears in the specification. If the Patent Office feel that the Applicant is in error, it is respectfully requested that the Patent Office point out the line in the Abstract wherein the words "means" or "said" allegedly occur. For all these reasons, the Patent Office's objection to the Applicant's Abstract is based upon factual error and should be withdrawn.

III. 35 U.S.C. § 112, Second Paragraph

Claims 1-34 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The test for definiteness is whether "the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits,

the courts can demand no more." *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). In *Hybritech*, the basis of the district court's holding that the plaintiff's claims were indefinite is that "they do not disclose how infringement may be avoided because antibody affinity cannot be estimated with any consistency." *Hybritech*, 231 USPQ at 94. The Federal Circuit reversed the district court's holding and found the claims definite under the above-recited test for definiteness, stating that "the evidence of record indisputably shows that calculating affinity was known in the art at the time of filing, and notwithstanding that those calculations are not precise, or 'standard,' the claims read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits." *Hybritech*, 231 USPQ at 94-95. The Applicant respectfully submits that she will show, in the analysis that follows, that claims 1-34 are definite under the *Hybritech* test.

(Claims 1-9)

In the present case, the Patent Office rejects claims 1-9 for indefiniteness, based upon the Applicant's use of the common everyday term "or" to introduce an alternative. However, unlike in *Hybritech*, where the definiteness of a "term of art" (*i.e.*, "affinity") was at issue, the present case involves the everyday term, "or" which has a singular and thus "definite" meaning:

> **or** a coordinating conjunction introducing an alternative; specif., a) introducing the second of two possibilities *[*beer *or* wine*]* b) introducing any of the possibilities in a series, but usually used only before the last *[*apples, (*or*) pears, *or* plums*]* .
>
> [Exhibit C: Webster's New World Dictionary, Second College Edition, D. Guralnik, Ed., Prentice Hall Press, 1986 at page 999.]

Thus, in the present case, one skilled in the art, upon reading the Applicant's claims, would understand what was meant by them, including their use of the common and everyday word "or." For this reason, this basis for rejection of claims 1-9 under 35 U.S.C. § 112, second paragraph, for indefiniteness is legally erroneous and should be withdrawn.

The Patent Office's rejection of claims 1-9 based upon the Applicant's use of "or" to indicate the alternative in claim 1 is legally erroneous for a second reason. In particular, the Patent Office suggests that the Applicants use the Markush terminology "being selected from the group consisting of" instead of "or". However, the courts have long recognized that the use of "or" is acceptable to indicate the alternative:

> In the PTO, one of the changes that took place was the **abandonment of the rule against the use of "or" in an enumeration of alternative materials** that might be used in a claimed invention, which rule was the basis of the objection to the decision giving rise to the Markush decision.
>
> [*In re Harnish*, 206 USPQ 300, 304 (CCPA 1980); emphasis added in bold.]

Thus, the courts have long recognized the acceptability in claims of the word "or" to introduce an alternative in the claims. Moreover, the Patent Office specifically discloses the use of "or" as being acceptable to indicate alternatives in multiple dependent claims:

> ***A. Acceptable Multiple Dependent Claim Wording***
>
> claim 16. A gadget as in claims 1, 7, 12, **or** 15, further comprising ---
>
> [MPEP at 608.01(n), page 600-64 (Rev. 1, Feb. 2000); emphasis added in bold.]

The Applicant respectfully submits that the Patent Office cannot have it both ways. The word "or" cannot be definite in one context, such as indicating claim dependency in the alternative, and be indefinite in another context when it has the same meaning. Finally, the Applicant cites to recently issued U.S. Pat 6,096,320 (Potter), which discloses a composition wherein one of the components is a "fragment" recited as an alternative by the word "or":

> A vaccine **composition** comprising an immunogenic chimeric protein that comprises **gamma-interferon** (γIFN), **or** an active **fragment thereof**, linked to at least one epitope of a leukotoxin derived from Pasteurella haemolytica, **and a pharmaceutically acceptable vehicle**.
>
> [Exhibit D: U.S. Pat. 6,096,320 at claim 1; emphasis added in bold.]

Thus, not only do those skilled in the art understand the meaning of the word "or" to designate alternatives (instead of a Markush group), but the courts recognize the use of "or", the MPEP demonstrates that the Patent Office understands what is meant by the use of "or" in a claim, and recently issued U.S. Pat. 6,096,320 demonstrates that the practice of the Patent Office is to allow the use of "or" to designate alternatives (including "fragments thereof") in composition claims. For all these reasons, the rejection of claims 1-9 under 35 U.S.C. § 112, second paragraph, for indefiniteness is legally erroneous and should be withdrawn.

(Claims 10, 17 and their dependents)

The Patent Office also contends that claims 10 and 17 and their dependents are indefinite "as to the effect of the end result of the recited treatment" and that it is not apparent from the claims "what the step of **administering** consists of." [Official Action at page 3; emphasis added in bold.] The Patent Office asks "What for

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example, are the conditions of "safe". [Official Action at page 3.] While it is submitted that one skilled in the art understands what is meant by "safe", the Applicants have amended independent claim 10 to delete reference to "safe". Accordingly, this basis for rejection of claim 10 and its respective dependents, has been rendered moot. Claim 17 does not recite the term "safe". Accordingly, this basis for rejection is not applicable to claim 17 or its dependents.

The administering step of Applicant's independent claim 10, as amended herein, now recites as follows:

> **administering a therapeutically effective amount** of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof to one or more coronary vessels or to a peripheral vein in a human patient in need of treatment for coronary artery disease.
>
> [Claim 10; emphasis added in bold.]

The Applicant respectfully submits that the phrase "**administering a therapeutically effective amount**" of a pharmaceutical agent is a well recognized phrase that is used in patent claims in the pharmaceutical arts that does not require a further definition in the claims to be understood, upon reading the Applicant's specification. In particular, the specification expressly discloses what is meant by the phrase "a therapeutically effective amount of recombinant FGF-2. . ." as recited in the administering step:

> Typically, the safe and **therapeutically effective amount** of the method of the present invention comprises 0.2 μg/kg to 48 μg/kg of rFGF-2 or an angiogenically active fragment or mutein thereof in a pharmaceutically acceptable carrier. In other embodiments, the safe and **therapeutically effective amount** comprises 0.2 μg/kg to 2 μg/kg, >2 μg/kg to <24 μg/kg, or 24 μg/kg to 48 μg/kg of rFGF-2 or an angiogenically active fragment or mutein thereof in a pharmaceutically acceptable carrier. In absolute terms, the safe and **therapeutically effective amount** is about .008 mg to about 7.2

> mg of rFGF-2 or an angiogenically active fragment or mutein thereof; more typically, 0.3 mg to 3.5 mg of rFGF-2 or an angiogenically active fragment or mutein thereof. A suitable rFGF-2 is the rFGF-2 of SEQ ID NO: 2 or an angiogenically active fragment or mutein thereof.
>
> [Specification at page 23, lines 3-14; emphasis added in bold.]

Thus, the phrase "**administering a therapeutically effective amount**" is definite because "the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and . . . the language is as precise as the subject matter permits. . . ." *Hybritech*, 231 USPQ at 94-95.

Moreover, the Applicant's specification expressly discloses to those skilled in the art what is meant by "**administering** a therapeutically effective amount of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof **to one or more coronary vessels or to a peripheral vein in a human patient** in need of treatment for coronary artery disease." In particular, the specification expressly discloses various methods for "administering" the unit dose composition of FGF-2, including by "intravenous ('IV') or intracoronary ('IC') injection or infusion". [Specification at page 17, line 29.] In addition, the specification teaches that "the unit dose composition of the present invention is administered via a cardiac catheter or other injection device. . . ." [Specification at page 20, lines 14-16.] At page 22, lines 10-20, the specification discloses a method for administering a unit dose of FGF-2 by "intracoronary (IC) infusion." Similarly, at page 22, lines 21-25, the specification discloses a method for administering a unit dose of FGF-2 by "intravenous (IV) infusion." Methods for selecting veins or coronary arteries for infusion of FGF-2 are disclosed in the specification at page 22, lines 3-9. One embodiment of the step of administering the unit dose composition, using a femoral or subclavian artery, is disclosed in the specification at page 24, line 2 to page 25, line 2. Thus, the "**administering**" step of claim 10, which specifically recites that the FGF-2 is being

For all these reasons, the rejection of claims 10 and 17, and their respective dependents, under 35 U.S.C. § 112, second paragraph, for indefiniteness is legally erroneous. The withdrawal of this basis for rejection is requested.

(Claims 19-21)

The Patent Office contends that "[c]laims 19-21 are indefinite for reciting '**therapeutic benefit**', because it is unclear what the benefit is or how much change is considered to be beneficial **since it is not defined in the claim**." [Official Action at page 4; emphasis added in bold.] In response, the Applicant has amended claim 19 to recite what the therapeutic benefit is, *i.e.*, "a therapeutic benefit **against coronary artery disease**". The Applicant respectfully submits that the "change" associated with a "therapeutic benefit" need not be "defined in the claims" as asserted by the Patent Office. A search of the U.S. Patent Office's database on U.S. Patents that have claims reciting the phrase "therapeutic benefit" is attached hereto as Exhibit E. Exhibit E lists 48 U.S. patents that have issued since 1976 with claims that recite a "therapeutic benefit". As reflected in the most recently issued of these 48 U.S. patents, the most common recitation is that the "therapeutic benefit is against [the disease being treated]." *See* Exhibit F: U.S. Pat. 6,090,810 (Klein) at claim 32 ("A **method of treating a pathological condition** in a mammal, said condition associated with a retinoic acid receptor activity, said method comprising administering to said mammal a retinoid antagonist or negative hormone capable of binding to a retinoic acid receptor subtype selected from the group consisting of RAR_α, RAR_β and RAR_γ, said antagonist or negative hormone being administered in an amount pharmaceutically effective to provide a **therapeutic benefit against said pathological condition** in said mammal . . ."); and Exhibit G: 6,001,847 (Daugan) at claim 13 ("A method of treating conditions where inhibition of cGMP-specific PDE is of **therapeutic benefit**, in a human or nonhuman animal body, which comprises administering to said body a therapeutically

effective amount of a compound having a formula . . ."). Thus, claim 19, as amended, and claims 20-21, which ultimately depend therefrom, are definite under the *Hybritech* test because they not only use conventional claim language, but "the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits. . . ." *Hybritech*, 231 USPQ at 94-95. In addition, the specification contains a plethora of disclosures expressly teaching one skilled in the art what is meant by the phrase "**therapeutic benefit**" against coronary artery disease. In particular, the specification teaches that these therapeutic benefits against coronary artery disease include an increase in exercise tolerance time (ETT), and improvements in the SAQ and in MRI of the target areas:

> The unexpected magnitude and duration of the **therapeutic benefit** that was provided to human patients in need of **coronary angiogenesis** by the unit dose composition and method of administration was seen as early as two weeks after the single unit dose was administered, and persisted for 6 months after the single unit dose was administered IC or IV, as determined by measuring **art-recognized clinical endpoints** such as **ETT**, the "**Seattle Angina Questionnaire**" **(SAQ)** and **MRI** of the target areas of the heart.
>
> [Specification at page 6, lines 13-20; emphasis added in bold.]

The **therapeutic benefit** provided to the **ETT** is fully discussed throughout the specification, including at page 6, line 20 to page 7, line 4. The **therapeutic benefit** provided to the **SAQ**, which assesses quality of life, is fully discussed throughout the specification, including at page 7, lines 5-25. The **therapeutic benefit** provided to the **MRI** is fully discussed throughout the specification, including at page 7, line 26 to page 8, line 14. Thus, claims 19-21, as amended, are definite under the *Hybritech* test because "the claims, read in light of the specification, reasonably apprise those skilled

in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits. . . ." *Hybritech*, 231 USPQ at 94-95. For all these reasons, the withdrawal of this basis for rejecting claims 19-21 is requested.

(Claim 26)

The Patent Office also rejects claim 26 for allegedly being indefinite, contending that "it is not clear how the resultant angiogenesis is **limited to 'heart'** absent isolation of the product administered solely to the heart." [Official Action at page 4.] The Applicant respectfully traverses.

In interpreting the meaning of the words of a claim, the courts have held as follows:

> It is entirely proper to use the specification to **interpret** what the patentee **meant by a word or phrase** in a claim. [citation omitted.] But this is not to be **confused** with **adding an extraneous limitation appearing in the specification**, which is improper. By "extraneous," we mean a limitation read into the claim from the specification wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim.
>
> [*E.I. Du Pont v. Phillips Petroleum*, 75 USPQ2d 1129, 1131 (Fed. Cir. 1988); emphasis added in bold.]

In the present case, the Applicant respectfully submits that the Patent Office is reading words of limitation (*i.e.*, that "angiogenesis is limited to the 'heart'") into claim 26 that are not present in claim 26. Claim 26 recites as follows:

> 26. A method for **inducing angiogenesis in a heart** of a human patient comprising, administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof to one or more coronary vessels or to a peripheral vein **in a human patient in need of treatment for**

coronary artery disease, said unit dose comprising from about .008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.

[Emphasis added in bold.]

Thus, upon reviewing the words of claim 26, the phrase "limited to" or "angiogenesis limited to heart" or a synonym thereof never appears in the claim. Accordingly, claim 26 cannot be held to be indefinite based upon words of limitation that never appear in the claim.

As a practical matter, the assignee of record has discovered that ischemic tissues are more responsive to angiogenic agents than the corresponding tissue in a normal environment because the ischemic tissues produce endogenous VEGF (a known angiogenic agent which interacts with FGF-2 to produce an enhanced angiogenic response). *See also* Harada *et al.*, *"Basic Fibroblast Growth Factor Improves Myocardial Function in Chronically Ischemic Porcine Hearts,"* J. Clin. Invest., **94**:623-630 (August 1994) which is cited as reference C18 of the Applicant's IDS dated 01/14/00. Harada discloses that "[b]asic FGF-stimulated angiogenesis is said to require an ischemic milieu, suggesting that the growth may be interacting with a variety of other mitogens to achieve this effect and that the ischemic conditions may result in upregulation of FGF receptor expression." [C18: Harada at page 627, col. 2.] Thus, "**in a human patient in need of treatment for coronary artery disease,**" the ischemic tissue of the heart would be more responsive to any angiogenic agent than would non-ischemic tissues exposed to the same concentration of angiogenic as occurs when administering FGF-2 (or an angiogenically active fragment or mutein thereof) into a peripheral vein. For these reasons, the rejection of claim 26 under 35 U.S.C. § 112, second paragraph, for indefiniteness based upon limitations not appearing in the claim is legally erroneous. The withdrawal of this basis for rejection is respectfully requested.

(Claims 30-34)

The Patent Office also contends that "[c]laim 30 is indefinite as to the resultant **effect** of the treatment." [Official Action at page 4; emphasis added in bold.] Claim 30 recites as follows:

> 30. A method for treating a human patient for a myocardial infarction comprising, administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof to one or more coronary vessels or to a peripheral vein in said human patient, said unit dose comprising from about .008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.

The test for definiteness is whether, "the claims, read in light of the specification, reasonably apprise those skilled in the art both of the **utilization** and **scope** of the invention, and if the language is as precise as the subject matter permits. . . ." *Hybritech*, 231 USPQ at 94-95. In the present case, the Patent Office does cannot say that claim 30 does not recite any utilization. On its face, claim 30 recites that it is directed to a "method for treating myocardial infarction." Thus, the utilization of claim 30 is "treating myocardial infarction". The "scope" of claim 30 comprises the step of "administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof to one or more coronary vessels or to a peripheral vein in said human patient, said unit dose comprising from about .008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof." The step that is recited in claim 30 is the same step that is recited in claims 17 and 26 for which no similar basis for rejection has been made. Moreover, at page 23, lines 10-11, the specification discloses that the amount of FGF-2 recited in claim 30 (*i.e.*, "about .008 mg to 7.2 mg") is a therapeutically effective amount. Thus, one skilled in the art

would understand the scope of claim 30. Accordingly, claim 30 satisfies the *Hybritech* test for definiteness because it reasonably apprises those skilled in the art of both the utilization and the scope of the invention and the language is as precise as the subject matter permits.

Separately, the Applicant respectfully submits that the claims are not required to recite the "effect" in a method for treating a particular disease. The Patent Office has not and cannot cite to any caselaw requiring the recitation of an "effect" as a requirement of definiteness. As examples of U.S. patents that recite a method for treating [a disease] comprising administering an "effective amount" of a [therapeutic agent] and not specifying an effect, the Applicant cites to the U.S. patents [Exhibits D, E and F] already made of record herein. In particular, U.S. Pat. 6,096,320 (Potter) [Exhibit D] recites in claim 11 the following method of treating a disease comprising the step of "administering" a medicament in "an effective amount," without reciting the "effect" produced by the medicament:

> 11. A **method of** preventing or ameliorating a **respiratory disease** comprising **administering** to a subject ruminant an **effective amount** of a vaccine composition according to claim 8.
>
> [Exhibit D: `320 at col. 52, lines 44-47; emphasis added in bold.]

U.S. Pat. 6,107,338 (Wos) [Exhibit H] recites in claim 16 the following method of treating a disease comprising an "administering" step which does not also recite an effect :

> 16. A **method of treating** a human or other animal subject having **a bone disorder**, said method comprising **administering** to said subject a compound according to the structure:
>
> . . . .

[Exhibit H: `338 at cols. 42-44; emphasis added in bold.]

U.S. Patent 6,096,697 (Wells) [Exhibit I] recites in claim 19 the following method of treating a disease comprising the step of "administering" a medicament in an "effective amount," without also reciting a specific "effect" produced:

> 19. A **method of treating skin** by **administering** a safe and **effective amount** of the compositions according to claim 1.
>
> [Exhibit I: U.S. Pat. 6,096,697 at col. 24, lines 8-9; emphasis added in bold.]

Thus, the above cited U.S. patents, all of which have issued in the last two months, establish that it is **not** a requirement for definiteness that a claim directed to a "method for treating a disease" which includes the step of "administering" a medicament, also recite the effect that is to be produced by the medicament. Those skilled in the art understand that the effect is amelioration of the disease being treated. Moreover, as shown above, the terminology used by the Applicant in claim 30 is conventional claim language for the pharmaceutical arts.

If Applicant wanted to claim the resultant effect, she would recite a method as in claim 26, which is directed to the effect, *i.e.*, "a method for inducing angiogenesis in a heart of a human patient. . . ." Along these same lines, the Applicant has added claim 35 by amendment herein which is directed to a "method for providing a human patient with relief from symptoms of angina . . . ."

Accordingly, the Applicant is entitled to claim a method for treating a disease, such as myocardial infarction, by administering an effective amount of a medication, without also indicating in the claim the effect produced by the medicament. For all these reasons, the rejection of claim 30 under 35 U.S.C. § 112, second paragraph, for indefiniteness for failing to recite a "resultant effect" is legally

erroneous and should be withdrawn. Likewise, claims 31-34, which were rejected based upon their dependency from claim 30, would not be indefinite.

IV. 35 U.S.C. § 102(b)

Claims 1-9 are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by U.S. Pat. 5,155,214 (Baird). According to the Patent Office, Baird discloses "substantially pure mammalian fibroblast growth factors"; "that basic FGF has similar activity in vivo on capillary endothelial cells [and] therefore, basic FGF is considered an angiogenic factor (see column 1)"; "pharmaceutical compositions including bFGF, a bFGF analog, biologically active fragments of bFGF or of analog bFGF, or nontoxic salts thereof dispersed in a pharmaceutically acceptable liquid or solid carrier" and the sequence of SEQ ID NO: 2 of the present invention." [Official Action at pages 4-5.] The Applicant respectfully disagrees that Baird is anticipatory of claim 1 and its dependents (claims 2-9).

Claim 1 of the present invention is directed to "[a] unit dose composition for inducing angiogenesis in a human, comprising about .008 mg to about 7.2 mg of FGF-2 or an angiogenically active fragment or mutein thereof in a pharmaceutically acceptable carrier." While Baird discloses a bFGF that has the amino acid sequence of SEQ ID NO: 2, Baird fails to disclose the "unit dose composition" of claim 1 (*i.e.*, a pharmaceutical composition) with all of its recited elements in the recited amounts (".008 mg to about 7.2 mg") for inducing angiogenesis in a human. For this reason alone, Baird is not anticipatory.

V. 35 U.S.C. § 103(a)

Claims 1-34 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Baird, in view of Sellke (Soc. of Thoracic Surgery, 65:1540-1544, 1992) and Uchida (Am. Heart J., 130(6): 1182-1188, Dec. 1995). According to the

Patent Office, the teachings of Baird are applied herein as applied in relation to claims 1-9 above. Independent claim 1 is directed to "a unit dose composition for inducing angiogenesis in a human . . . ." Independent claim 10 is directed to "a method for treating a human patient for coronary artery disease. . . ." Independent claim 17 is directed to a method for treating a human patient for coronary artery disease comprising, administering a single unit dose . . . ." Independent claim 26 is directed to "a method for inducing angiogenesis in a heart of a human patient . . . ." Independent claim 30 is directed to "a method for treating a human patient for a myocardial infarction . . . ." The Patent Office has admitted that "Baird et al. do not expressly teach a method of for [sic] treating coronary heart disease or myocardial infarction." [Official Action at page 6.] To make up for this deficiency, the Patent Office cites to Sellke for disclosing "results and technical considerations of the administration of basic fibroblast growth factor for the induction of collateral growth using heparin-alginate slow-release **devices** in patients undergoing coronary artery by pass grafting." [Official Action at page 6; emphasis added in bold.] However, as pointed out by the Patent Office, Sellke is directed to the use of "**devices**". In contrast, the present invention is directed to a **unit dose pharmaceutical composition**. Moreover, Sellke discloses that his devices, which contain either 1 or 10 μg of bFGF, require surgical **implantation** into the cardiac tissue in lots of **ten** (10):

> After all distal anastomoses were completed, **ten heparin-alginate beads** each containing 1 or 10 μg of bFGF (10 μg or 100μg of total bFGF, respectively) were **implanted** into the **epicardial fat** or **subepicardium** in the nongraftable myocardial region in pockets through 2- to 3-mm stab incisions.
>
> [Sellke at 1541, col. 2; emphasis added in bold.]

Sellke discloses that his device provides for "**slow, continuous**" dosing of bFGF:

> In this study, we demonstrated that that the **slow, continuous release** of bFGF using heparin alginate devices is technically feasible and safe.
>
> [Sellke at page 1542, col. 2; emphasis added in bold.]

By "slow, continuous release" of bFGF, Sellke means the **continuous release** of a very low dosage (30 or 300 ng/day) of bFGF over a period of **"3 to 4 weeks"**:

> The **release** of bFGF from heparin-alginate beads is under first-order kinetics, at a rate of approximately **30 or 300 ng/day**, and **complete after 3 to 4 weeks**.
>
> [Sellke at page 1541; col. 2; emphasis added in bold.]

Thus, Sellke discloses a surgically implantable device having bFGF immobilized therein on heparin-alginate, that when implanted in aggregates of 10, provides for the **continuous release** of low amounts (30 ng/day or 300 ng/day) of bFGF directly into the epicardial fat or subepicardium in which the device is implanted. In contrast, the "unit dose composition" of the present invention provides an amount of FGF-2 ("about .008 mg to about 7.2 mg") that is in a form (unit dose composition) that is available for **immediate release** into the vasculature of the patient, and that when administered as a **unit dose** into the vasculature of a patient having an ischemic heart disease, provides the patient with a therapeutic effect. Sellke's disclosure that his surgically implantable **continuous release** composition and device is "technically feasible and safe" [Sellke at page 1542, col. 2] leads one skilled in the art in a divergent direction (**continuous release composition/device/implantation**) from the path (**unit dose composition/intravascular administration**) taken by the Applicant, and therefor "**teaches away**" from the present invention as a matter of law. *See Monarch Knitting v. Sulzer*, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998) ("A prior art reference may be considered to teach away when 'a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or **would be led**

in a direction divergent from the path taken by the applicant'"); emphasis added in bold.

The final reference relied upon by the Patent Office is Uchida. However, like Sellke, Uchida also teaches away from the unit dose composition and methods of the present invention. In particular, the Patent Office cites to Uchida for disclosing that "angiogenesis and myocardial salvage [in dogs] occur as illustrated by injection through the right atrium into the pericardial cavity of **30 mg basic fibroblast growth factor** and 3 mg heparin sulfate." [Official Action at pages 6-7 (bridging sentence); emphasis added in bold.] In contrast, the compositions and methods of the present invention employ "**about .008 mg to about 7.2 mg of FGF-2** or an angiogenically active fragment or mutein thereof." Thus, on its face Uchida discloses the use of an FGF-2 composition that has a substantially higher concentration (4x to 4000x) of FGF-2 than is employed in the unit dose composition of the present method.

Further, the direction taken by Uchida diverges from the path taken by the Applicant because Uchida discloses administering **high concentrations** of FGF-2 by **intrapericardial** injection, whereas the Applicant claims administering one or more **substantially lower doses** ("about .008 mg to about 7.2 mg of FGF-2") by **intracoronary of intravenous** injection. One skilled in the art also recognizes that the modes of administration chosen by Uchida and by the Applicant differ greatly. In particular, Uchida's method injects FGF-2 into the pericardial space, which is a closed space, whereas the Applicant's method injects (substantially lower dosages) into the vasculature which is open to the entire body. Because the pericardial space is a closed space, Uchida's method **bathes** the myocardium with the bFGF enriched pericardial fluid for a **sustained period** of time. Thus, Uchida's method is analogous to Sellke's method because both methods provide for **continuous (or sustained) dosing** of the myocardium. In contrast, the Applicant's method provides the myocardium with a bolus dose of FGF-2 on one or more occasions, *i.e.*, a dose that rapidly decreases in concentration as the dose

is disseminated throughout the circulation and taken up by the body. Thus, like Sellke, Uchida leads one skilled in the art in a divergent direction (**a high concentration FGF-2 composition/intrapericardial administration/continuous dosing**) from the path (**a low concentration FGF-2 unit dose composition/intravascular administration/bolus dosing**) taken by the Applicant, and therefore "**teaches away**" from the Applicant's invention as a matter of law. *See Monarch Knitting v. Sulzer*, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998) ("A prior art reference may be considered to teach away when 'a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or **would be led in a direction divergent from the path taken by the applicant**'"); emphasis added in bold.

Thus, the Patent Office has admitted that "Baird *et al.* do not expressly teach a method of for [sic] treating coronary heart disease or myocardial infarction." [Official Action at page 6.] The Applicant has shown that Sellke and Uchida do not make up for this deficiency because they teach away from the Applicant's invention, *i.e.*, "a person of ordinary skill, upon reading the reference[s] . . . **would be led in a direction divergent from the path taken by the applicant.**" *See Monarch*, 45 USPQ2d at 1984. As a matter of law, it is "error to find obviousness where references 'diverge from and teach away from the invention at hand.'" *In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988). For these reasons, the rejection of claims 1-34 under 35 U.S.C. § 103(a) over Baird, Sellke and Uchida if legally erroneous and should be withdrawn.

CONCLUSION

Claims 1-34 stand rejected. Claims 35-37 have been added by amendment herein. Accordingly, claims 1-37 are pending.

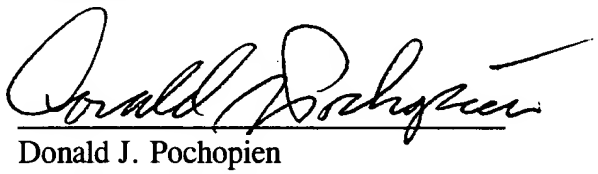
In view of the arguments and evidence herein, all bases for objection to the specification and the Abstract have been rendered moot. In view of the arguments and

evidence herein, all bases for rejection of claims 1-34 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite have been rebutted. In view of the arguments and evidence herein, the rejection of claims 1-9 under 35 U.S.C. § 102(b) has been shown to be factually erroneous. In view of the teaching away by the cited art, all bases for rejection of claims 1-34 under 35 U.S.C. § 103(a) have been shown to be legally erroneous.

For the above cited reasons, these bases for rejection should not be applied against newly added claims 35-37. Accordingly, claims 1-37 are in condition for allowance. The allowance of claims 1-37 is respectfully requested.

Respectfully submitted,

McANDREWS, HELD & MALLOY, LTD.

By: 

Donald J. Pochopien
Registration No. 32,167
Attorney for Applicants
500 West Madison Street
34th Floor
Chicago, Illinois 60661
(312) 707-8889

Dated: September 15, 2000
J:\chiron\uspto\1543.004 Amend & Res 1.111.doc

US 093851140DP1

Creation date: 02-01-2005
Indexing Officer: VPHAN - VU PHAN
Team: OIPEBackFileIndexing
Dossier: 09385114

Legal Date: 11-30-2000

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